c) a nucleotide sequence encoding the polypeptide linker is formed by two partially overlapping PCR primers during a PCR reaction that links the first variable domain and the second variable domain; and wherein

d) the compound has a bivalent or a multivalent structure.

REMARKS

Claims 1-13 and 25-33 are currently under examination. Claims 14-22 have been removed from consideration. Applicants have amended claim 1 to further describe and clarify the claimed invention. Support for this amendment is found in the specification's original claims, at page 2, lines 25-28 and in Examples 1-3. Thus, this amendment does not introduce new matter. Applicants now respond to each of the current rejections according to its statutory section.

Rejections Under 35 U.S.C. § 112

The Office rejects claim 5 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter not described in the specification. Specifically, the Office requests that Applicants demonstrate that the L6 antibody or the hybridoma that produces the L6 antibody are publicly available. Applicants referred to Hellström *et al.* (PNAS 83:7059 (1986); "Hellström 1") and Hellström *et al.* (Cancer. Res. 46:3917-23 (1986); "Hellström 2") as demonstrating that the L6 antibody was publicly available. Hellström 1 used the L6 antibody as a reagent while Hellström 2 documents the genesis of the L6 antibody. The Office notes that there is no evidence to show that either of these journals have a policy requiring authors to provide their reagents to the public.

Applicants attach here evidence obtained from the web site for the Proceedings of the National Academy of Sciences (PNAS), which requires all authors to "make

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

UNIQUE MATERIALS (e.g., cloned DNAs, antibodies, . . .) promptly available on request by qualified researchers . . . ." Item (viii) under Journal Policies (emphasis in original). Applicants note that this item does not specify a minimal time period during which these materials must be available. Thus, they are presumably available indefinitely from the time the journal publishes the article onward. Applicants need not deposit the L6 antibody or its hybridoma because it is publicly available by virtue of the Hellström 1 article. Applicants request that the Office withdraw its rejection of claim 5.

Claims 1-13 and 25-33 remain rejected under 35 U.S.C. § 112, first paragraph, because, according to the Office, they are not enabled for any and all internal linkers. The Office, referring to page 3 of Applicants' previous response, alleges that Applicants have "admitted on the record that no one could provide internal linkers of the *claimed* construct without undue experimentation." Page 3 of current Office Action, lines 7-10, emphasis added. Applicants have admitted no such thing, as discussed below.

At page 3 of the previous response, Applicants distinguished between the two types of linkers present in the claimed compound. The first linker attaches the two variable regions to each other and is internal to the antigen binding region. The second linker attaches the enzyme to the antigen binding region, which is comprised of the two variable regions linked together. Applicants clarified the invention by indicating that claim 1 referred to the second linker and cited ample evidence in the specification to enable the use of such linkers. In no way do Applicants' statements suggest that the use of the first linker would require undue experimentation. Rather, Applicants' explanation at page 3 pertained to the second linker because the word "linked" in claim 1 refers to the second linker. As such, the Office's rejection of claim 1 and its

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

dependent claims for allegedly not enabling use of various internal linkers is irrelevant, as internal linkers are not recited in the claim. Rather, claim 1 recites an "antigen binding region."

To clarify the invention, Applicants have amended claim 1 to recite the internal linker that joins both variable domains. The specification enables a skilled artisan to use many different potential linker sequences to join the two variable regions. In Example 2, the specification instructs that the two PCR primers used to generate the 3' end of the V_H segment (i.e., linker-anti primer) and the 5' end of the V_L segment (i.e., linker-sense primer) are partially complementary to each other. Based on this general description, a skilled artisan can easily generate similar primers that provide overlap with each target V region segment and contain complementary regions, thus allowing overlap during PCR to generate a complete antigen binding region. Tables 2 and 3 provide examples of such primers and indicate the level of complementarity between them, which is about 50 percent. Applicants therefore request that the Office withdraw its rejection of claims 1-13 and 25-33, as they are enabled by the specification.

The Office rejects claims 1-13 and 25-33 under 35 U.S.C. § 112, first paragraph, because as previously amended, claim 1 allegedly introduces new matter. To facilitate prosecution, Applicants have amended claim 1 to recite "antigen binding regions [that] consist of a single polypeptide chain . . . ." Applicants contend that claim 1 no longer introduces new matter and request that the Office withdraw this rejection.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

Rejections Under 35 U.S.C. § 102

Claims 1-4, 8-9, 25-26, and 33 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Winter *et al.* (U.S. Patent 6,248,516). According to the Office,

Winter teaches constructs containing single domain ligands including sFvs, which may be linked to an effector molecule. Winter also allegedly teaches that multiple single domains can also be linked to an effector molecule.

As discussed above, Applicants have amended claim 1 to clarify the invention. Claim 1 provides that the two variable domains in the antigen binding domain are connected by a polypeptide linker. On the nucleotide level, the two polynucleotides that encode the two variable domains are linked by two overlapping PCR primers, that during PCR, simultaneously connect the two variable domains and form the internal linker. Winter does not teach how to employ these methods to connect two variable domains into one single chain. Thus, Applicants assert that this reference does not anticipate the claimed invention and request that the Office withdraw its rejection.

Rejections Under 35 U.S.C. § 103

The Office sets forth several rejections of the pending claims under 35 U.S.C. § 103(a). First, it maintains its rejection of claims 1-9, 25-27, 30, and 33 under 35 U.S.C. § 103(a) as allegedly unpatentable over Bosslet *et al.* (Brit. J. Can. 1992) or Seeman *et al.* (EP 0501215) in view of Huston *et al.* (U.S. Pat. No. 5,132,405), and as necessary, Bosslet *et al.* (EP 0040097) and Eaton *et al.* (EP 0392745).

Second, claims 1-2, 9, 11, 12, 31, and 32 stand rejected as allegedly obvious over the above references an in further view of Ong *et al.* (Can. Res. 1991), Bagshawe *et al.* (WO 89/10140) and Huston *et al.* (Meth. Enz. 1991).

Third, the Office rejects claims 1, 10, 13, and 29 under all the references cited in the first two rejections and in further view of Goochee *et al.* (Biotechnol. 1991).

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

Fourth, claims 1, 6, and 28 stand rejected in view of Bosslet or Seeman, in view of Huston, and as necessary Bosslet and Eaton and in further view of Bagshawe *et al.* (WO 88/07178).

Finally, the Office rejects claims 1-4, 8, 9, 25, 26, and 33 as allegedly obvious over Winter. As noted in Applicants' previous response, all of the above rejections involve claim 1 and all of the other pending claims are dependent on claim 1. Applicants will thus continue to address these rejections in the context of that claim. Applicants respectfully traverse the Office's rejections on the following grounds.

First, Applicants note that, in its enablement rejection, the Office independently asserts that a skilled artisan would need to exercise undue experimentation to determine how to use the internal linker. This position is inconsistent with Office's rejection of the pending claims as allegedly obvious. Specifically, the Office believes that sFv and Fab fragments are functionally equivalent and as such it would have been obvious to use an sFv fragment to replace the Fab fragments in Bosslet and Seeman's constructs. The Office's assertion that undue experimentation is required to arrive at an sFv fragment argues against its obviousness. Further, Fab fragments are not structurally equivalent to sFv fragments. Thus, a compound containing an sFv would not be obvious in light of a references that supposedly teaches Fab fragments.

Second, the Office contends that Huston teaches that the sFv may be fused to an enzyme and believes that one would have readily envisioned the enzyme being encoded by the same strand encoding the antigen binding domain. *See* Office Action, page 5, lines 8-10. As provided in the specification, an enzyme may also be linked to the antigen binding domain by chemical means. *See* page 4, lines 30-33. As there are

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

alternative methods for linking an enzyme to an antigen binding domain, Applicants do not agree that a skilled artisan would have "readily" considered encoding the enzyme by the same nucleic acid. Rather, those in the art may have considered chemical linking as well.

Third, the Office asserts that "since Huston et al. teach that antibodies can be engineered to provide sFv constructs within antigen biding activity, there is no reason to consider that Seeman . . . or Bosslet et al. teach away from forming sFv . . . constructs." Office Action page 6, line 19 to page 7, line 2. Applicants respectfully contend that the Office's reasoning is flawed. *Arguendo*, even if the Office correctly characterized Huston's teaching, the fact that Seeman and Bosslet both indicate that their construct should be made so that the tumor binding portion should be as similar as possible to the original antibody indicates that the art was undecided in how to generate such constructs. A skilled artisan, reading Seeman and Bosslet (two references teaching away from a single polypeptide chain), and Huston (only reference allegedly teaching toward a single polypeptide chain), would detect the existing confusion in the literature and likely decide to follow the majority thinking in the field. At the least, this conflict does not make using a single polypeptide chain to express both variable regions obvious.

Finally, Applicants continue to assert that none of the references cited by the Office provide any motivation to combine their teachings as described by the Office. As discussed above, Seeman and Bosslet teach away from the claimed invention. Huston teaches away from using constructs that contain any constant region sequence. The Office has asserted that the claimed invention does not include constructs with constant

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

regions. See Office Action, page 7, lines 8-10. Contrary to the Office's belief, the claimed invention does include constant region sequences. As described in Example 3, in the pMCG-E1 construct, the first small box after the HindIII site is the V_H leader sequence, the next box is the V_H variable domain followed by the internal linker and the next hatched box, which is the V_L variable domain. The next small box in that construct is a CH1 exon followed by the hinge region. See also the full paragraph at page 13 of the specification. None of these references in combination make the claimed invention obvious.

Furthermore, the Office's justifications as to why the cited references should be combined are based on general conclusions about knowledge in the art. Such conclusory statements may not be used to support a rejection based on obviousness. *See In re Lee*, 277 F.3d 1338 (Fed. Cir. 2002) (holding that conclusory statements based on general knowledge or common sense cannot be used to overcome deficiencies of a reference). As such, the Office has not demonstrated how any of the cited references provide the motivation to combine them. Applicants therefore request that the Office withdraw the above rejections under 35 U.S.C. § 103(a).

Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of claims 1-13 and 25-33.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: July 12, 2002

By: Carol P. Einaudi

Carol P. Einaudi
Reg. No. 32,220

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com